UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,317	05/31/2005	Sunil Shaunak	POLYT 9351 WO-US	3774

39843 7590 01/20/2010

BELL & ASSOCIATES
58 West Portal Avenue No. 121
SAN FRANCISCO, CA 94127

EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
01/20/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

abell@bell-iplaw.com
mkaser@bell-iplaw.com
info@bell-iplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/511,317	SHAUNAK ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,48-51,and 54-139* is/are pending in the application.

4a) Of the above claim(s) *50,56-58,62,70,74-77,81,88-91,99 and 103-139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,48,49,51,54,55,59-61,63-69,71-73,78-80,82-87,92-98 and 100-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

The amendment filed on October 26, 2009 is acknowledged. Claims 2-47 and 52-53 have been canceled and claims 50, 56-58, 62, 70, 74-77, 81, 88-91, 99, and 103-139 have been withdrawn. Claims 1, 48-49, 51, 54-55, 59-61, 63-69, 71-73, 78-80, 82-87, 92-98, and 100-102 are under examination in the instant office action.

Applicants' arguments, filed on October 26, 2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Responses are limited to Applicants' arguments relevant to either reiterated or newly applied rejections.

Election/Restrictions

In response to request for reconsideration of the restriction requirement, once the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully

examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

With regard to the elected species, glucosamine 6-sulphate was examined in the previous office action mailed on 5/26/2009 as evidenced by prior art rejections.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 48-49, 51, 54-55, 59-61, 63-69, 71-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed,

had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims recite a generic genus, *i.e.*, generic glycodendrimer comprising monosaccharide carbohydrate moieties covalently linked to a carboxylic terminated dendrimer.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic

acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

Applicants provide no description of the claimed generic glycodendrimer, either in word, by structure, by formula, by chemical name, or by physical properties that would indicate that Applicants were in possession of the claimed generic glycodendrimer at the time of the invention. The only disclosed examples of dendrimer and carbohydrate moiety is a carboxylic terminated poly(amidoamine) dendrimer (PAMAM dendrimer) generation 3.5 and glucosamine or modified glucosamine such as glucosamine 6-sulphate in the specification, they are not representatives of species falling within the scope of the claimed genus since the term "glycodendrimer" was interpreted as a designation for carbohydrate-containing molecules which can be grown generationwise following an iterative repetitive synthesis and there are various types of dendrimers other than PAMAM dendrimer (see Rockendorf *et al.* cited above). In addition, Applicants do not describe the structural features of such glycodendrimer that would possess the claimed activity.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The

specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Response to Applicant's argument:

Applicants argued that the dendrimer is defined by its structural characteristics, in that it is carboxylic terminated and the instant specification discloses different types of dendrimers. In response to the argument, the structural characteristic, "carboxylic terminated", explains only the terminal part of the whole molecule of the dendrimer, but does not define the whole structure of the dendrimer. Furthermore, the instant specification provides only two examples of carboxylic terminated dendrimers (PAMAN and DAB), however they are not representatives of species falling within the scope of the claimed genus since "carboxylic terminated" dendrimers encompass any highly branched macromolecules with carboxylic-termini and there are various types of dendrimers depending on repetitive base molecule. In addition, there is no prior art recognizing that the claimed genus of carboxylic terminated dendrimers are well-known to one of ordinary skill in the art at the time of the present invention. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 48-49, 51, 54-55, 59-61, 63-69, 71-73, 78, 80, 82-87, 92-98, and 100-102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PAMAM generation 3.5-glucosamine or glucosamine modified with sulfate or acetyl group, does not reasonably provide enablement for the other glycodendrimers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (Balls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All factors have been considered together and specifically relevant factors are addressed below:

The nature of the invention and the breadth of the claims: The claims are drawn to a generic glycodendrimer comprising carbohydrates moieties linked to a carboxylic terminated dendrimer. The "glycodendrimer" encompasses carbohydrate-containing molecules which can be grown generationwise following an iterative repetitive synthesis and there are various types of dendrimers depending on repetitive base molecule. In addition, carbohydrate moiety attached to

the dendrimers encompasses any monosaccharides. Thus, the number of theoretically conceivable glycodendrimers as claimed is in thousands rendering the scope of the claims large.

The state of the prior art: Generally, the relative skill of those in the art of pharmaceuticals and pharmacology are high. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant composition for accomplishing the desired result of the claimed invention without undue experimentation. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

The predictability or unpredictability of the art: Malik *et al.* (J controlled Release 65:133-148, 2000) teaches that dendrimers are highly branched macromolecules of low polydispersity that provide many exciting opportunities for design of novel drug-carriers, gene delivery systems and imaging agents and hold promise in tissue targeting applications, controlled drug release (abstract). They disclosed several dendrimer including amine terminated dendrimers (cationic dendrimer) and carboxylic acid terminated dendrimer (anionic dendrimer), which were used to study systematically the effect of dendrimer generation and surface functionality on biological properties in vitro (abstract, table 1, and figure 1). They show that dendrimers have huge difference in molecular weight and the number of surface groups depending on the generation, that is, the higher generation has the higher molecular weight and the more surface groups (Table I). In addition, their study shows that cytotoxic or haemolytic effects and bio-distribution of dendrimers vary depending on type of repetitive base molecules and generations. For example,

anionic PAMAM dendrimers (gen 2.5, 3.5 and 5.5) showed longer circulation times (~20–40% recovered dose in blood at 1 h) with generation-dependent clearance rates; lower generations circulated longer. While polyether dendrimers bearing carboxylate are haemolytic, the anionic PAMAM and DAB dendrimers were not haemolytic up to concentration of 2 mg/ml, but the higher generation carboxylate PAMAMs were (Fig 4 and p142, col 2, para2). These data provide evidence that depending on the generation and types of repetitive base molecule, different types of dendrimers have different biocompatibility, thus one of ordinary skill in the art would not expect that any generation of dendrimer or any type of dendrimers based on different repetitive base molecule would have similar biological activities as claimed. It is unpredictable what specific embodiment of the thousand possibilities of the instant claims would have the desired biological properties. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The amount of direction or guidance presented and the presence or absence of working examples: The only disclosed working example of dendrimer and carbohydrate moiety is a carboxylic terminated poly(amidoamine) dendrimer (PAMAM dendrimer) generation 3.5 and glucosamine or modified glucosamine such as glucosamine 6-sulphate in the specification (fig. 1b). However, they are not representatives of species falling within the scope of the claimed genus as stated above. Furthermore there is no information about how many molecules of monosaccharide carbohydrate are attached to a dendrimer. In addition, Applicants do not describe the structural features of such glycodendrimer that would possess the claimed activity. Applicants disclosed *in vitro* assays showing the effects of dendrimer generation 3.5 –

glucosamine 6-sulfate (31-60), however, there is no disclosure regarding other types of glycodendrimers with regard to "how to make" and "how to use" aspects.

The Quantity of Experimentation Needed. Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a glycodendrimer out of the plethora of possibilities encompassed by the instant claims that would have desired biological properties.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

Response to Applicant's argument:

Applicants argued that the number of theoretically conceivable glycodendrimer is relatively low and the breadth of the claims limited since the scope of claim 1 as amended no longer encompasses glycodendrimers derived from di-, tri-, or oligo-saccharides, saccharides that do not contain an amino group, or dendrimers which are not carboxylic-terminated. However, the scope of claim 1 is still broad since carboxylic-terminated dendrimers encompass any highly branched macromolecules with carboxylic-termini and there are various types of dendrimers depending on repetitive base molecule.

Also, Applicants argued that it is highly predictive for the pharmaceutical use for the instant composition based on the disclosure of the instant specification. However, Applicants only disclosed *in vitro* assays showing the effects of dendrimer generation 3.5 –glucosamine 6-sulfate (31-60) and there is no disclosure regarding other types of glycodendrimers with regard to "how to make" and "how to use" aspects. In addition, there is no prior art recognizing that the claimed genus of carboxylic terminated dendrimers are well-known to one of ordinary skill in the art at the time of the present invention and the pharmaceutical use of the claimed genus of carboxylic terminated dendrimers would be predictable. Furthermore, prior art recognized unpredictable nature in the art of carboxylic terminated dendrimers. Malik *et al.* show that cytotoxic or haemolytic effects and bio-distribution of dendrimers vary depending on type of repetitive base molecules and generations. Anionic PAMAM dendrimers (gen 2.5, 3.5 and 5.5) showed longer circulation times (~20–40% recovered dose in blood at 1 h) with generation-dependent clearance rates; lower generations circulated longer. While polyether dendrimers bearing carboxylate are haemolytic, the anionic PAMAM and DAB dendrimers were not haemolytic up to concentration of 2 mg/ml, but the higher generation carboxylate PAMAMs were. These data provide evidence that depending on the generation and types of repetitive base molecule, different types of dendrimers have different biocompatibility, thus one of ordinary skill in the art would not expect that any generation of dendrimer or any type of carboxylic terminated dendrimers having different repetitive base molecule would have similar biological activities as claimed. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Accordingly, the instant claims still do not comply with the enablement requirement of

35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

In response to applicant's argument that Malik *et al.* contain s no teaching regarding certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., immuno-modulatory properties of glycodendrimer) are not recited in the rejected base claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 48-49, 51, 54-55, 59-61, 63-69, 71-73, 78-80, 82-87, 92-98, and 100-102 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rockendorf *et al.* (Topics in Current Chemistry, 217: 2001) in view of Malik *et al.* (J controlled Release 65:133-148, 2000, supplied by Applicants) and US 2003/0114418 (pub date: 6/19/2003, effective filing date: 8/14/2001).

Rockendorf *et al.* teaches glycodendrimers, which have become valuable tools in glycobiology especially in the context of multivalency which is an important principle of carbohydrate-protein interactions (abstract). It further teaches that sugarcoated noon-carbohydrate dendrimers, which serves as a scaffold for the multiple presentation of sugar moieties, which are known as the principal carbohydrate epitopes in particular glycobiological systems (p205, para 1). Also, it teaches that the phenomenon of multivalency adds to the strength of carbohydrate-protein interaction that is needed for a significant biological effects and thus the week affinity of singular interacting is multiplied to an overall avidity with binding constants in the nanomolar range (p205, para 2). The multivalent glycodendrimers are

developed as glycomimetics to interfere carbohydrate-protein interaction, wherein protein-carbohydrate complexation is important in a wide range of medically significant interactions including signal transduction, inflammation, and microbilogical pathogenesis (p207, para 2). It discloses various types of glycodendrimer such as a cationic polyamidoamine (PAMAM) dendrimer functionalized (covalently linked) with carbohydrate moiety in the periphery (p203, para 3 and figure 1 and 7) and N-acetyl-glucosamine-functionalized dendrimers (scheme 2 and p209, para 1).

The reference differs from the instant claims insofar as it does not specifically teach glucosamine 6-sulfate linked to PAMAM dendrimer generation 3.5 and the concentration of glycodendrimer. In addition, it is silent about treating severe sepsis recited in claims 61, 63-65, 69, 71-73, 80, and 82-84 and decreasing chemokine or cytokine level and decreasing angiogenesis recited in claims 92-97.

Malik *et al.* teaches that dendrimers are highly branched macromolecules of low polydispersity that provide many exciting opportunities for design of novel drug-carriers, gene delivery systems and imaging agents and hold promise in tissue targeting applications, controlled drug release (abstract). They disclosed several dendrimer including amine terminated PAMAM dendrimers (generation 1-4) and carboxylic acid terminated PAMAM dendrimer (generation 1.5, 2.5, 3.5, 5.5, 7.5, and 9.5), which were used to study systematically the effect of dendrimer generation and surface functionality on biological properties *in vitro* (abstract, table 1, and figure 1). The study shows that cationic dendrimers such as PAMAM dendrimers bearing -NH_2 termini were generally haemolytic and cytotoxic dependent on molecular weight (generation) and the number of surface groups displaying IC_{50} values 50–300 μg/ml dependent on dendrimer-type,

cell-type and generation (abstract) while anionic dendrimers such as PAMAM dendrimer bearing carboxylic termini were neither haemolytic nor cytotoxic over a broad concentration range up to concentration of 2 mg/ml (2000 μg/ml) (abstract, p142, col 2, para 2, and table 3). It further teaches that for a polymeric carrier to be suitable for *in vivo* application it is essential that the carrier is nontoxic and nonimmunogenic, and it should preferably be biodegradable (p134, col 2, para 2). In addition, it disclosed an specific use of PAMAM generation 3.5 as a drug carrier for tumor targeting such as PAMAM generation 3.5–palatinate, which is able to selectively increase the platinum content of palpable B16F10 subcutaneous tumors approximately 50-fold compared to that seen after i.v. administration of cisplatin at its maximum tolerated dose (p146, col. 2, para 2).

US 2003/0114418 teaches a method of treating inflammation or inflammation-associated disorder by administrating glucosamine in combination with cyclooxygenase 2-selective inhibitor, wherein the glucosamine is selected from the group consisting of glucosamine, glucosamine salts of hydrochloric, iodic, sulfuric, phosphoric, or other pharmaceutically acceptable acid; glucosamine-2-sulfate; glucosamine -3-sulfate; glucosamine -6-sulfate; glucosamine -2,3-disulfate; glucosamine- 2,6-disulfate; glucosamine -3,6-disulfate; glucosamine-3,4,6-trisulfate; glucosamine pentaacetate; glucosamine-1-phosphate; glucosamine-6-phosphate; N-acetylglucosamine-6-phosphate; N-acetylglucosamine-1-phosphate; N-acetyl-D-glucosamine; uridine diphosphate (UDP)-N-acetylglucosamine; and mixtures thereof (claims 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use carboxylic termiated PAMAM dendrimer generation 3.5 taught by Malik *et al.* as a drug delivery carrier of glucosamine derivatives such as glucosamine 6-sulfate

in order to make a non-cytotoxic and biocompatible glycodendrimer because of the following reasons: Dendrimers have been taught to be useful carriers for therapeutic agents by prior art. Rockendorf *et al.* already discloses a polyamidoamine (PAMAM) dendrimer functionalized (covalently linked) with carbohydrate moiety in the periphery and N-acetyl-glucosamine-functionalized dendrimers. Malik *et al.* teaches that cationic dendrimers were generally haemolytic and cytotoxic dependent on molecular weight (generation) and the number of surface groups while anionic dendrimers such as PAMAM dendrimer bearing carboxylic termini were neither lytic nor cytotoxic over a broad concentration range. Thus, the skilled artisan would have been motivated to modify the glycodendrimers taught by Rockendorf *et al.* by using PAMAM dendrimer bearing carboxylic termini, which are less cytotoxic and haemolytic compared to cationic PAMAM dendrimer. In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute any glucosamine derivative such as glucosamine 6-sulfate for N-acetyl-glucosamine since they are known to be functional equivalent as taught by US 2003/0114418.

With regard to the concentration of glycodendrimer, one of ordinary skill in the art at the time of invention would have been motivated to optimize the concentration of glycodendrimer based on IC_{50} values of PAMAM dendrimers taught by Malik *et al.* in order to avoid cytotoxic and haemolytic effects. The effective dosage of the composition of the present invention can be determined according to age, gender, severity of condition, absorption of an active ingredient, dosage forms, types of vehicles used with the active ingredients, inactivation rate, excretion and other medicines applied together. In addition, it is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ

33; *In re Russell*, 169 USPQ 426. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

With regard to treating severe sepsis recited in claims 61, 63-65, 69, 71-73, 80, and 82-84 and decreasing chemokine or cytokine level or decreasing angiogenesis recited in claims 92-97, the instant invention is directed to a product or a composition, thus an intended use, which are treating severe sepsis, decreasing chemokine or cytokine level or decreasing, does not have a patentable weight. In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be new. If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statutes make no provision for patenting of an article or composition which is not, in and of itself, new.

Response to Applicant's argument:

Applicants argued that there is no teaching in Rockendorf *et al.* of a glycodendrimer in which an amino sugar is covalently linked to a carboxylic terminated dendrimer by an amide bond between the amine group and a dendrimer carboxylic group. In response to this argument, one cannot show nonobviousness by attacking references individually where the rejections are

based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the previous action mailed on 5/26/2009, Rockendorf *et al.* already discloses a polyamidoamine (PAMAM) dendrimer functionalized (covalently linked) with carbohydrate moiety in the periphery and N-acetyl-glucosamine-functionalized dendrimers and Malik *et al.* teaches that anionic dendrimers such as PAMAM dendrimer bearing carboxylic termini were neither lytic nor cytotoxic over a broad concentration range while cationic dendrimers were generally haemolytic and cytotoxic dependent on molecular weight (generation) and the number of surface groups. Thus, the skilled artisan would have been motivated to use PAMAM dendrimer bearing carboxylic termini taught by Malik *et al.* instead of cationic dendrimers taught by Rockendorf *et al.* in order to make a non-cytotoxic and biocompatible glycodendrimer. When PAMAM dendrimer bearing carboxylic termini is used for as a drug delivery carrier of glucosamine derivatives such as glucosamine 6-sulfate in view of the prior art in combinations, the skilled artisan would have reasoned that the carboxylic group of PAMAM dendrimer be covalently linked to the amine group of glucosamine derivatives such as glucosamine 6-sulfate by an amide bond since it is well-known to make a covalent bond via an amide bond between a carboxylic group and the amine group of glucosamine derivatives as evidenced by Lam *et al.* (J. Polym, Res., vol. 6 (4): 203-210, 1999, Figure 2).

In response the argument that Malik *et al.* teaches that introduction of amine functionality into anionic dendrimers was required to facilitate further functionalisation of the dendrimer, Malik *et al.* teaches introduction of an amine into PAMAM dendrimer to allow radioiodination for detection of body distribution, however the reference do not teach that "introduction of amine

functionality into anionic dendrimers was required to facilitate further functionalisation of the dendrimer".

In response the argument regarding unexpected result, the alleged unexpected result is not claimed as a range or by functional language, thus Applicant's possible unexpected result is not commensurate with the scope of the claimed invention. In addition, a mere statement of unexpected result without evidence is not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., immuno-modulatory and anti-inflammatory properties of glycodendrimer) are not recited in the rejected base claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00-6:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614
Bbs

BONG-SOOK BAEK
Examiner, Art Unit 1614